ACTION OF TRIFLUOROACETIC ANHYDRIDE AND HEPTAFLUOROBUTYRIC ANHYDRIDE ON AMIC ACIDS

By

PARSHOTAM LAL BHATIA

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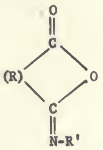
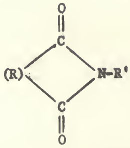
I. INTRODUCTION

The isoimides* (unsymmetrical imides) I are a class of compounds which are isomeric with and similar to n-imides (symmetrical imides) II in their chemical properties. Corresponding members of these two classes differ from each other in their physical properties, but the isolation of isoimides is relatively recent while the imides have been known a long time.



I



II

$R = (CH_2)_n$, C_2H_2, or o-C_6H_4

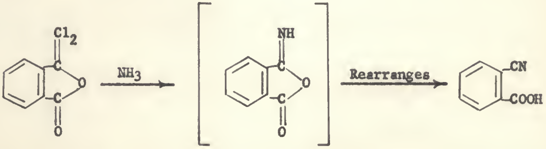
R' = Aryl or alkyl

Phthalisoimides

In 1892 the first evidence of the existence of phthalisoimides was reported in the literature by Hoogewerff and van Dorp.[1] They obtained o-cyanobenzoic acid by the action of ammonia on phthalyl chloride. Since neither phthalimide, nor phthaldiamide could be transformed by ammonia into o-cyanobenzoic acid, they assumed that an unsymmetrical phthalimide was formed as an intermediate compound, which was unstable in alkaline solution and rearranged to the acid, thus:

---

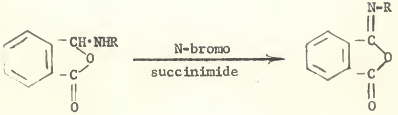
*The name "isoimide" is used as a class name, adding the usual prefix to indicate the parent acid: e.g., maleisoimide, rather than iso-maleimide. This is consistent with the nomenclature of imides and amic acid and lessens the confusion with acids, the names of which include the prefix iso.



phthalyl chloride phthalisoimide o-cyanobenzoic acid

The possibility that these isoimides could exist led the same workers to synthesize them. Between 1893 and 1895, they claimed to have prepared camphorisoimides (α and β), N-methylcamphorisoimides (α and β), N-ethylcamphorisoimides (α only), N-benzylcamphorisoimides (α only), hemipinisoimides (α and β), N-methylphthalisoimide, and N-benzylphthalisoimide from their respective amic acids using acetyl chloride or phosphorus oxychloride as dehydrating agents.[2,3,4]

In 1896 van der Meulen[5] prepared N-phenylphthalisoimide by the action of acetyl chloride on phthalanilic acid (N-phenylphthalamic acid). These results were duplicated by other investigators. Nothing substantial was done from 1896 until 1957, when Carpino[6] showed that oxidation of the hydrazones and oximes of phthalaldehydic acid by means of N-bromosuccinimide yields phthalisoimides. He also reported the infrared spectra for the carbonyl region of the phthalimides and phthalisoimides prepared in the course of his work. In all cases he found that the isoimides absorbed at 1705-1658 cm.$^{-1}$ (5.85-6.03).

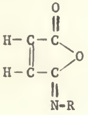


R = $NHCOOCH_2C_6H_5$ or OH

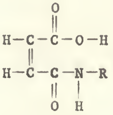
In 1960 the author[7] prepared a series of phthalisoimides from the amic acids using trifluoroacetic anhydride as a dehydrating agent.

Maleisoimides

The first attempt reported in the literature in the preparation of maleisoimides was made by Piutti[8] in 1910. He claimed the preparation of N-(p-methoxyphenyl)-maleisoimide (III, R=$p\text{-}CH_3O\text{-}C_6H_4$) and N-(p-ethoxyphenyl)-maleisoimide (III, R=$p\text{-}C_2H_5O\text{-}C_6H_4$), by acetyl chloride dehydration of the corresponding maleamic acids, IV.



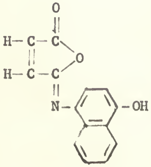
III



IV

Roderick[9] showed that the compounds obtained by Piutti did not possess the maleisoimide structure but instead were α-chloro-N-(p-alkoxyphenyl)-succinimides.

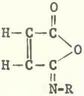
Tsou, Barnett and Seligman[10] dehydrated N-(4-hydroxy-1-naphthyl)-maleamic acid with trifluoroacetic anhydride and obtained N-(4-hydroxy-1-naphthyl)-maleisoimide, V. This was, therefore, the only substantiated example of a maleisoimide in the literature, since their attempts to prepare other maleisoimides using trifluoroacetic anhydride were unsuccessful.



V

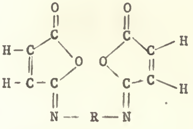
In 1960, the author[7] prepared N-(p-methoxyphenyl), N-(p-ethoxyphenyl), and N-p-tolyl-maleisoimides from their respective amic acids using trifluoroacetic anhydride as a dehydrating agent.

In 1961, Cotter, Sauers, and Whelan[11] reported the preparations of N-butyl, N-phenyl, N-o-tolyl, and N-o-chlorophenyl-maleisoimides III, N,N'-hexamethylenebismaleisoimide VI, and bis(4-N-phenyl-maleisoimido)-methane VI from their corresponding amic acids using dicyclohexylcarbodiimide, ethyl chloroformate-triethylamine, trifluoroacetic anhydride-triethylamine, and acetic anhydride-triethylamine as dehydrating agents.



Isoimide III

R = butyl, phenyl, o-tolyl,
o-chloro-phenyl



Bis-isoimide VI

R = hexamethylene,
$-C_6H_4-CH_2-C_6H_4-$

II. PURPOSE

A. Effects of Nitro Substituents, Unsaturation, and Steric Factors

In a previous study on the synthesis of isoimides, the author[7] prepared several new isoimides by the dehydration of N-arylphthalamic and N-arylmaleamic acids using trifluoroacetic anhydride as the dehydrating agent. N-(p-methoxyphenyl)-, N-(p-chlorophenyl)-, N-(o-chlorophenyl)-, N-p-tolyl-, and N-o-tolyl-phthalamic acids were dehydrated to their respective isoimides. Isoimides were also obtained from N-(p-methoxyphenyl)-, N-(p-ethoxyphenyl)-, and N-p-tolyl-maleamic acids. No isoimides could be obtained from N-phenyl- and N-(p-methoxyphenyl)-succinamic acids; instead N-phenyl succinamic acid formed succinic dianilide while N-(p-methoxyphenyl)-succinamic acid was recovered unchanged.

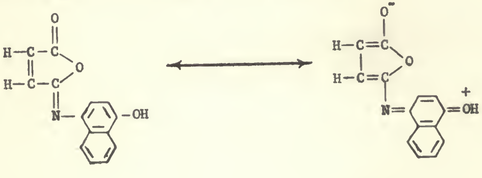
It was observed in the above study that with electron donating groups in the ortho and para positions of the benzene ring in N-arylphthalamic and maleamic acids, it is easier to form an isoimide, while this does not seem to hold in the case of saturated amic acids, where the isoimide could not be obtained at all either from N-phenyl-substituted or N-(p-methoxyphenyl)-substituted acids.

One of the purposes of this study was to complete the series of isoimides; in particular, it was decided to apply a strong electron withdrawing substituent, such as the nitro group, and a strong electron donating substituent, such as the dimethylamino group, to the benzene ring in N-arylamic acids. It was also decided to investigate the requirements for formation of these isoimides with regard to steric factors, such as the size of the ring formed, and with regard to electronic factors such as unsaturation present in the acid moiety. In particular, it was desired to prepare isoimides of saturated acids, of which only the camphorisoimides have been reported.

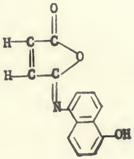
B. Isoimide from a Saturated Acid

The author, while studying the effect of trifluoroacetic anhydride on N-arylsuccinamic acids, found that these acids could not be dehydrated to isoimides by this reagent. Tsou[10] was able to prepare N-(4-hydroxy-1-naphthyl)-maleisoimide Va and Vb but not N-(5-hydroxy-1-naphthyl)-maleisoimide VIIa and VIIb. He proposed that this difference might be due to the lack of resonance in N-(5-hydroxy-1-naphthyl)-maleisoimide. N-phenylsuccinamic acid and N-(p-methoxyphenyl)-succinamic acid likewise would form isoimides VIIIa and VIIIb which would not be stabilized by resonance, owing to the lack of a double bond between carbon atoms a and b.

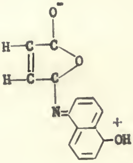
The forms Va and Vb both contribute to the actual structure, but structures VIIb and VIIIb are of very little importance and do not contribute significantly to the actual structures.



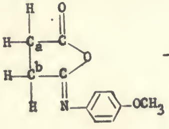
Va Vb



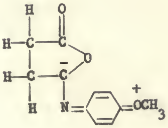
VIIa



VIIb

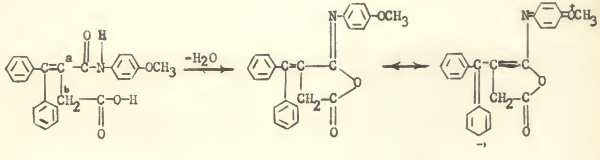


VIIIa



VIIIb

In order to investigate further the effect of unsaturation in the acid moiety, it was decided to study the effect of trifluoroacetic anhydride on a compound of the succinic series (lacking a double bond between carbon atoms a and b) which would give a resonance-stabilized isoimide IXa. N-(p-methoxyphenyl)-γ, γ-diphenylitaconamic acid IX was selected for the study as it was easy to prepare and satisfied the above conditions.



IX IXa Isoimide (6 forms)

C. Dehydration Studies

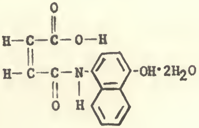
Since all electron donating substituents on the benzene ring in N-aryl amic acids appear to facilitate the formation of isoimides, it was desired to study quantitatively the effect of various substituents by measuring the rate of dehydration of several amic acids.

D. Interpretation of Infrared Data

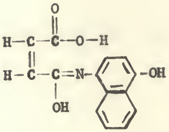
Although a good deal of work has been done on the position of C=N stretching absorption in various classes of compounds, the information available is often indecisive. Bellamy[12] quotes the range 5.95-6.13μ for the stretching frequency of the C=N band in unsaturated compounds. All of the isoimides prepared by Carpino[6] absorbed in the regions 5.49-5.60μ (C=O) and 5.86-6.03μ (C=N). Tsou[10] in the course of his study reported that N-(4-hydroxy-1-naphthyl)-maleisoimide gave two strong bands at 5.57μ (C=O) and 5.99μ (C=N). Cotter[11] recently reported that all the maleisoimides prepared by him absorbed at 5.58μ (C=O) and 5.94μ (C=N). Since infrared spectra have been employed as the primary method of identification of isoimides, both in this study and in the previous study, a summary and discussion of the infrared absorption of the isoimides prepared was a very important purpose of this study.

E. Attempted Studies on the Detection of Enolic Form

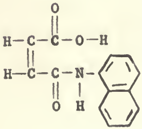
Tsou,[10] in attempting to account for the colors of hydrated N-(4-hydroxy-1-naphthyl)-maleamic acid (X, yellow) and its anhydrous form (Xa, red), has suggested that the anhydrous form might exist in the enolic form, which would show a deeper color due to an extended conjugated system of unsaturation. He also reported that the infrared spectrum of the anhydrous acid had a conspicuous absence of the 1639 cm.$^{-1}$ (6.1μ) band (amide) whereas a strong amide band was observed in the spectra of the compounds of the types XI and XII.



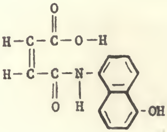
X Yellow



Xa Red

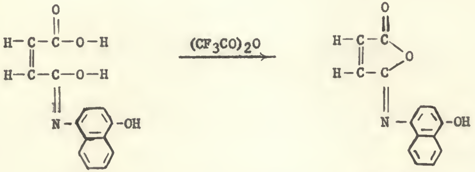


XI



XII

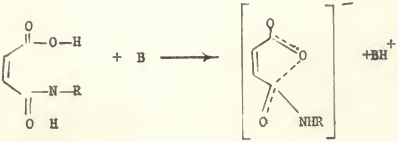
The ultraviolet spectra of these compounds also show significant differences in that Xa has a split maximum at 209 and 237 mμ whereas XI and XII each have a single maximum at 222 mμ. These observations led Tsou to suggest that the lactim form Xa exists, and that it is the lactim form which is converted to the isoimide by trifluoroacetic anhydride.



Xa

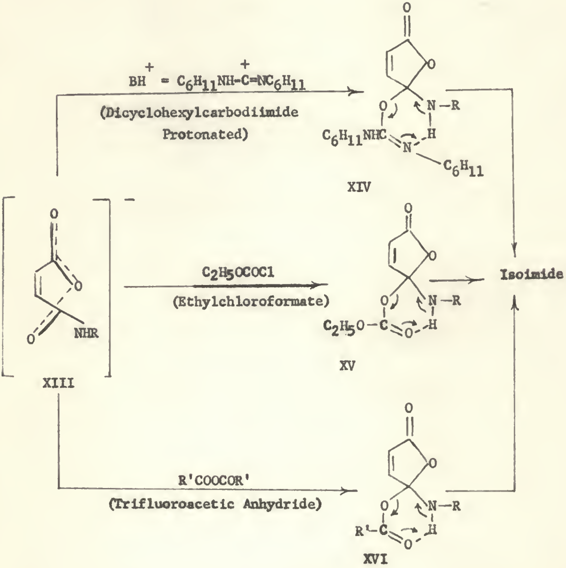
Isoimide

Cotter, et al. do not believe that the reaction follows the above path. They have reported that the dehydrations of N-substituted maleamic acids by N,N'dicyclohexylcarbodiimide, ethyl chloroformate-triethylamine, trifluoroacetic anhydride-triethylamine, and acetic anhydride-triethylamine probably proceed by similar mechanisms but ones which do not involve the enolic form. According to them, the maleamic acid first donates a proton to the base, a cyclic intermediate XIII being formed. Further reactions with the dehydrating agents could lead to the species XIV, XV, and XVI,which could decompose via the indicated quasi six-membered ring transition states into the maleisoimide.



Maleamic acid XIII

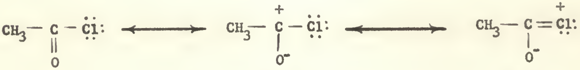
B = Triethylamine or N, N'dicyclohexylcarbodiimide ($C_6H_{11}N{=}C{=}NC_6H_{11} + H^+ \longrightarrow$ $C_6H_{11}NH\text{-}\overset{+}{C}{=}NC_6H_{11}$ or BH^+)



Since this pathway is possible only when there is a base present (triethylamine or dicyclohexylcarbodiimide), it is difficult to explain how the reaction could take place in the absence of the base, as the author has prepared all the isoimides using only trifluoroacetic anhydride. In an attempt to obtain further evidence which might aid in determining whether the reaction proceeds through the enolic form Xa or through a ring closure structure XIII it was hoped to detect any enolic form in nuclear magnetic resonance and infrared spectra of the amic acids.

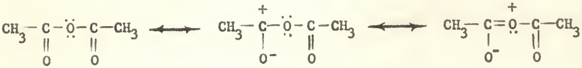
F. Action of Heptafluorobutyric Anhydride on Amic Acids

It is a well-known fact that acid chlorides are better acylating agents than acid anhydrides. This is due to the fact that the halogen atom exerts a strong inductive effect in acid chlorides, whereas in acid anhydrides, the resonance effect of the acetate group is more important, as shown in XVIIa, b, and c and XVIIIa, b, and c. For acid chlorides, form XVIIc is not important, while for acid anhydrides all three forms are quite important. Though acid chlorides are better acylating agents and hence better dehydrating agents than acid anhydrides,



$$CH_3-\underset{\underset{O}{\|}}{C}-\ddot{\underset{\cdot\cdot}{Cl}}: \longleftrightarrow CH_3-\overset{+}{\underset{\underset{O^-}{|}}{C}}-\ddot{\underset{\cdot\cdot}{Cl}}: \longleftrightarrow CH_3-\underset{\underset{O^-}{|}}{C}=\overset{+}{\underset{\cdot\cdot}{Cl}}:$$

XVIIa XVIIb XVIIc



$$CH_3-\underset{\underset{O}{\|}}{C}-\ddot{\underset{\cdot\cdot}{O}}-\underset{\underset{O}{\|}}{C}-CH_3 \longleftrightarrow CH_3-\overset{+}{\underset{\underset{O^-}{|}}{C}}-\ddot{\underset{\cdot\cdot}{O}}-\underset{\underset{O}{\|}}{C}-CH_3 \longleftrightarrow CH_3-\underset{\underset{O^-}{|}}{C}=\overset{+}{\underset{\cdot\cdot}{O}}-\underset{\underset{O}{\|}}{C}-CH_3$$

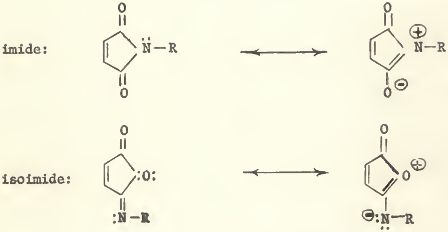
XVIIIa XVIIIb XVIIIc

they suffer from one great disadvantage, namely, that they release hydrogen chloride when they act as acylating or dehydrating agents and this hydrogen chloride combines with isoimides to form isoimide hydrochlorides. These hydrochlorides are unstable in the presence of moisture, which causes hydrolysis to the original amic acids and thus makes the isolation of isoimides difficult. The acid anhydrides are therefore preferable to acid chlorides as dehydrating agents in the preparation of isoimides.

Since trifluoroacetic anhydride did not effect dehydration of succinamic acids, it was desired to employ a stronger dehydrating agent. Trifluoroacetyl chloride is a more effective acylating agent and hence should be a stronger dehydrating agent, but in addition to the problem of working with a gas, the reagent suffers from the above mentioned disadvantage. It appeared that heptafluorobutyric anhydride might be a stronger dehydrating agent, and it was employed in an attempt to dehydrate succinamic acids to isoimides. Because of the interesting and unexpected products obtained from the action of heptafluorobutyric anhydride on succinamic acids, it was decided to study the action of this reagent on each of the other types of amic acid as well.

G. Basicity of Isoimides

Hoogewerff, while preparing isoimides from different phthalanilic acids using acetyl chloride as a dehydrating agent, observed that these isoimides formed hydrochlorides; the free isoimides were obtained by the addition of base. This property has been utilized for the purification of camphorisoimides.[2] Imides are not basic and do not form hydrochlorides. Comparison of the electronic formulas of imides with those of isoimides readily indicates the greater electron density at the nitrogen atom of the isoimide.



The action of hydrogen chloride on maleisoimides was therefore studied, since this property of maleisoimides has not been previously examined, to see whether maleisoimides are as strongly basic as the phthalisoimides.

III. EXPERIMENTAL*

I. Preparation of New Amic Acids, Imides, and Related Compounds

A. Phthalic Series

N-(p-Dimethylaminophenyl)-phthalamic acid.—A solution of 4.5 g. (0.033 mole) of freshly distilled p-dimethylphenylenediamine in 10 ml. of benzene was slowly added to a solution of 4.0 g. (0.033 mole) of phthalic anhydride in 50 ml. of benzene. A whitish yellow solid separated at once. The suspension was cooled and filtered and the precipitate was washed with benzene. The crude acid was purified by dissolving it in 30 per cent sodium dicarbonate solution, from which it was reprecipitated by the addition of dilute hydrochloric acid until the solution was just acid. An excess of mineral acid should be avoided. The white-grey precipitate, which separated slowly on stirring, was collected and crystallized from 95 per cent alcohol. Yield: 5.0 g. (53 per cent), m.p. 261-64 degrees.

Anal. calcd. for $C_{16}H_{16}N_2O_3$: C, 67.61; H, 5.63; N, 9.86;
Found: C, 67.60; H, 5.50; N, 10.02.

N-(p-Methoxyphenyl)-methylphthalamate.—Fifty ml. of an ethereal solution of diazomethane (0.01 mole) was added slowly to 2.7 g. (0.01 mole) of N-(p-methoxyphenyl)-phthalamic acid in 60 ml. of ether. After the addition was complete, the mixture was stirred for 15 minutes. The white precipitate that separated was filtered and crystallized from aqueous acetone to give white shining plates. Yield: 2.3 g. (82 per cent), m.p. 143-47 degrees.

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*All melting points are uncorrected.

Anal. calcd. for $C_{14}H_8O_4N_2$: C, 62.69; H, 2.98; N, 10.45;
Found: C, 62.56; H, 3.03; N, 10.60

B. Maleic Series

N-(p-Dimethylaminophenyl)-maleamic acid.—To a solution of 5.0 g. (0.05 mole) of maleic anhydride dissolved in 50 ml. of dry ether was added very slowly 6.8 g. (0.05 mole) of p-dimethylphenylenediamine in 15 ml. of ether, and the flask was cooled under tap water occasionally. A scarlet precipitate which separated on cooling was filtered and washed with a little ether. The crude acid was purified by solution in 30 per cent sodium bicarbonate solution, from which it was reprecipitated by dilute hydrochloric acid until it was just acid. It was crystallized from 95 per cent alcohol. Scarlet crystals. Yield: 9.7 g. (83 per cent), m.p. 212 degrees.

Anal. calcd. for $C_{12}H_{14}N_2O_3$: C, 61.55; H, 5.98; N, 11.96;
Found: C, 61.18; H, 5.20; N, 11.68.

N-(p-Dimethylaminophenyl)-maleimide.—A mixture of 1.0 g. (0.0042 mole) of N-(p-dimethylaminophenyl)-maleamic acid, 10 ml. of acetic anhydride, and 5.0 g. of anhydrous sodium acetate was refluxed for four hours. The solution was then cooled and poured onto crushed ice. The red-brown precipitate which separated at once was filtered, washed first with water and then with 10 per cent sodium bicarbonate solution to remove any unchanged acid. The crude product melted at 143-145 degrees and on crystallization from acetone gave reddish-brown crystals, Yield: 0.75 g. (80 per cent), m.p. 153-154 degrees.

Anal. calcd. for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.55; N, 12.96;

Found: C, 66.42; H, 5.65; N, 12.75.

C. Itaconic Series

N-(p-Methoxyphenyl)- -(diphenylhydroxymethyl)-succinamic acid.[*]— Five g. (0.0189 mole) of γ,γ-diphenylitaconic anhydride[14] was dissolved in 20 ml. of benzene, and 2.5 g. (0.0189 mole) of p-anisidine in 20 ml. of benzene was slowly added. To the clear solution, n-pentane was then slowly added, until a white semisolid on standing for some time in the open became solid. The solid dissolved readily in 10 per cent sodium bicarbonate solution, and on acidification of this solution with dilute hydrochloric acid, a white solid separated which on crystallization from dilute acetone gave white shining crystals. Yield: 3.6 g. (50 per cent), m.p. 138 degrees.

Anal. calcd. for $C_{24}H_{21}O_4N$ (Expected compound, N-(p-methoxyphenyl)-γ,γ-diphenylitaconamic acid): C, 74.42; H, 5.42; N, 3.61;

Found: C, 70.37; H, 5.66; N, 3.40.

But the calculated value for hydrated acid agrees with the observed values. Anal. calcd. for $C_{24}H_{23}O_5N$: C, 71.11; H, 5.67; N, 3.45. The infrared spectrum showed the presence of alcoholic OH, which further confirmed the formation of N-(p-methoxyphenyl)-β-(diphenylhydroxymethyl)-succinamic acid.

The acid is soluble in acetone, chloroform, dioxane, alcohol, benzene and insoluble in n-pentane and n-hexane. It decolorizes potassium permanganate solution slowly, which shows the absence of a double bond.

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[*] Alternate name: β-(Diphenylhydroxymethyl)-succin-p-anisidic acid.

N-(p-Methoxyphenyl)-γ,γ-diphenylitaconimide.—One g. (0.0024 mole) of N-(p-methoxyphenyl)-β-(diphenylhydroxymethyl)succinamic acid was heated in a porcelain dish until it melted. On cooling and washing with dilute sodium bicarbonate solution a white solid separated which on crystallization from aqueous acetone gave white crystals, m.p. 194-195 degrees. Yield: 0.43 g. (50 per cent).

Anal. calcd. for $C_{24}H_{19}O_3N$: C, 78.05; H, 5.15; N, 3.79;
Found: C, 77.98; H, 5.37; N, 3.93.

On refluxing N-(p-methoxyphenyl)-γ,γ-diphenylitaconimide with dilute sodium hydroxide for about thirty minutes, it gave γ,γ-diphenylitaconic acid. It is believed that N-(p-methoxyphenyl)-β-(diphenylhydroxymethyl)-succinamic acid is first formed which is further hydrolyzed to γ,γ-diphenylitaconic acid, because when N-(p-methoxyphenyl)-β-(diphenylhydroxymethyl)-succinamic acid itself was refluxed for thirty minutes with 10 per cent sodium hydroxide solution, p-anisidine, m.p. 52 degrees (reported 57 degrees), and γ,γ-diphenylitaconic acid, m.p. 120-122 degrees, were recovered.

D. Action of Hydrogen Chloride on Isoimides

One-half g. each of N-(p-methoxyphenyl)- and N-p-tolyl-maleisoimides[7] were dissolved in 20 ml. portions of anhydrous ether and dry hydrogen chloride was passed into the solutions. After one minute, thick orange-yellow precipitates began to appear in both cases. The precipitates were collected but apparently hydrolyzed on contact with atmospheric moisture. The melting point obtained for the product from N-(p-methoxyphenyl)-maleisoimide was 181 degrees (reported for amic acid 186 degrees) and that for the product from N-p-tolylmaleisoimide was 191 degrees (reported for amic acid 201 degrees). The products were soluble in dilute sodium bicarbonate solution and insoluble in water. When the above procedure was applied to N-(p-methoxyphenyl)- and N-p-tolyl-phthalisoimides, no precipitates could be obtained.

II. Action of Trifluoroacetic Anhydrides on Amic Acids

Previously known amic acids were in most cases prepared by mixing a solution of the acid anhydride with a solution of N-arylamine at room temperature. The solutions were prepared in ether, benzene, chloroform, or acetone, depending upon the solubility of the acid anhydride and N-arylamine. The amic acids in almost all cases precipitated in the cold. In some cases the methods cited in the literature were followed. The melting points and yields obtained were:

Phthalamic acids: N-(p-nitrophenyl), 192 degrees (85 per cent); N-(m-nitrophenyl), 202 degrees (80 per cent); N-(o-nitrophenyl), 149-151 degrees (83 per cent); N-(o-methoxyphenyl), 168-169 degrees (75 per cent). Maleamic acids: N-(p-nitrophenyl), 204 degrees (90 per cent); N-(m-nitrophenyl), 206 degrees (88 per cent); N-(o-nitrophenyl), 134 degrees (81 per cent). Malonamic acid: N-phenyl, 132 degrees (38 per cent). Succinamic acids: N-phenyl, 150 degrees (80 per cent); N-(p-methoxyphenyl), 168-169 degrees (81 per cent). Glutaramic acids: N-phenyl, 126-127 degrees (70 per cent); N-(p-methoxyphenyl), 143 degrees (78 per cent). Adipamic acid: N-phenyl, 149 degrees (20 per cent).

A. Phthalic Series

N-(p-Nitrophenyl)-phthalisoimide.—Five g. (0.0175 mole) of N-(p-nitrophenyl)-phthalamic acid[15] was dissolved in 50 ml. of dry dioxane. To this mixture 3 ml. (0.022 mole) of trifluoroacetic anhydride was added. The mixture was shaken and white shining crystals were obtained immediately. The crystals were filtered to give 2.3 g., m.p. 172 degrees. The filtrate when poured into 100 ml. of ice water, gave another crop of white precipitate. This precipitate was filtered, washed with water, and the unchanged acid was removed by keeping the solid in 10 per cent sodium bicarbonate solution for thirty minutes. On crystallization from acetone the white residue gave white shining crystals which also melted at 172 degrees. Total yield: 4.3 g. (91 per cent), m.p. 172 degrees.

Anal. calcd. for $C_{14}H_8O_4N_2$: C, 62.69; H, 2.98; N, 10.45;
Found: C, 62.49; H, 3.07; N, 10.58.

N-(m-Nitrophenyl)-phthalisoimide.—To 2.0 g. (0.007 mole) of N-(m-nitrophenyl)-phthalamic acid[15] in 30 ml. of dry dioxane was added 1 ml. of (0.007 mole) trifluoroacetic anhydride. The colorless solution was stirred for one hour. When the solution was poured into 50 ml. of ice water, a white precipitate was obtained. The precipitate was filtered, washed first with water and then with 10 per cent sodium bicarbonate solution to remove any unchanged acid. The light brown residue was crystallized from aqueous acetone. Light grey crystals, m.p. 138 degrees. Yield: 1.0 g. (50 per cent).

Anal. calcd. for $C_{14}H_8O_4N_2$: C, 62.69; H, 2.98; N, 10.45;
Found: C, 62.56; H, 3.03; N, 10.60.

N-(o-Nitrophenyl)-phthalisoimide.—Two g. (0.007 mole) of N-(o-nitrophenyl)-phthalamic acid[15] was suspended in 25 ml. of dry dioxane. To this suspension was gradually added 1 ml. (0.007 mole) of trifluoroacetic anhydride, and the mixture was kept for half an hour at room temperature and then poured into 100 ml. of ice water. The white precipitate was filtered and washed first with water and then with 10 per cent sodium bicarbonate solution. The residue was then crystallized from aqueous acetone to give white crystals, m.p. 162 degrees. Yield: 1.1 g. (60 per cent).

Anal. calcd. for $C_{14}H_8O_4N_2$: C, 62.69; H, 2.98; N, 10.45;
Found: C, 62.22; H, 3.16; N, 10.41.

N-(o-Methoxyphenyl)-phthalisoimide.—Five g. (0.0187 mole) of N-(o-methoxyphenyl)-phthalamic acid[16] was suspended in 60 ml. of dry dioxane. To this mixture, was added 2.5 ml. (0.0187 mole) of trifluoroacetic anhydride and the flask was cooled under tap water. The yellow solution was kept for one hour and was then poured into 100 ml. of ice water. The yellow precipitate, which did not solidify immediately, was filtered and washed with 10 per cent sodium bicarbonate solution to remove any unchanged acid. The deep yellow residue weighs 4 g. (87 per cent) which on crystallization from aqueous acetone gave fine, deep yellow crystals. Yield: 3.2 g. (70 per cent), m.p. 121-122 degrees.

Anal. calcd. for $C_{15}H_{11}O_3N$: C, 71.15; H, 4.21; N, 5.53;
Found: C, 71.26; H, 4.29; N, 5.62.

N-(p-Dimethylaminophenyl)-phthalisoimide.—Two g. (0.007 mole) of N-(p-dimethylaminophenyl)-phthalamic acid was dissolved in 30 ml. of dry dioxane. To this solution was slowly added 1.5 ml. (0.01 mole) of trifluoroacetic anhydride and the flask was cooled under tap water. The solution at once turned yellow and was kept for five minutes at room temperature. The yellow solution was poured into ice water and the yellow precipitate that separated was filtered and washed with water. It was kept in 30 per cent sodium bicarbonate solution to remove any unchanged acid. The residue was crystallized from aqueous acetone to give orange needles, m.p. 170 degrees. Yield 1.0 g. (55 per cent).

Anal. for $C_{16}H_{14}N_2O_2$: C, 72.18; H, 5.26; N, 10.52;
Found: C, 71.93; H, 5.59; N, 10.58.

B. Maleic Series

N-(p-Nitrophenyl)-maleisoimide.—To a suspension of 2.0 g. (0.0084 mole) of N-(p-nitrophenyl)-maleamic acid[17] in 30 ml. of dry dioxane was added approximately 1.5 ml. (0.01 mole) of trifluoroacetic anhydride at room temperature. The yellow solution was kept at room temperature for one hour. The solution was poured into 100 ml. of ice water, forming a light yellow precipitate. The precipitate was filtered and washed well with cold water. It was then kept in 10 per cent sodium bicarbonate solution to remove any unchanged acid. The yellow residue on crystallization from aqueous acetone gave light yellow needles, m.p. 110-112 degrees. Yield: 1.5 g. (80 per cent).

Anal. calcd. for $C_{10}H_6O_4N_2$: C, 55.04; H, 2.75; N, 12.84;
Found: C, 54.04; H, 2.74; N, 12.69.

N-(m-Nitrophenyl)-maleisoimide.—Two g. (0.0084 mole) of N-(m-nitrophenyl)-maleamic acid[17] was suspended in 30 ml. of dry dioxane. To this mixture was added 1.5 ml. (0.01 mole) of trifluoroacetic anhydride. The solution at once turned yellow and was mechanically stirred for one hour. It was then poured into 50 ml. of cold 10 per cent sodium bicarbonate solution.* The suspension of yellow oil which formed was extracted with ether. The ether solution was dried over sodium sulfate for 24 hours and the ether was removed under reduced pressure. The remaining liquid on standing in air gave yellow crystals, m.p. 57 degrees. Yield: 0.87 g. (50 per cent).

Anal. calcd. for $C_{10}H_6O_4N_2$: C, 55.04; H, 2.72; N, 12.84;
Found: C, 55.05; H, 2.79; N, 12.92.

On standing in air for three days, the isoimide hydrolyzed to the amic acid.

N-(o-Nitrophenyl)-maleisoimide.—Two g. (0.0084 mole) of N-(o-nitrophenyl)-maleamic acid[18] was suspended in 50 ml. of dry dioxane. To this mixture was added 1.5 ml. (0.01 mole) of trifluoroacetic anhydride, and the flask was cooled under tap water. The solution was kept for one hour and was then poured into 50 ml. of ice water. The light yellow precipitate which separated immediately was filtered and washed with 10 per cent sodium bicarbonate solution to remove any unchanged acid. The yellow residue on crystallization from aqueous acetone gave light yellow needles, m.p. 107-109 degrees. Yield: 1.4 g. (82 per cent).

Anal. calcd. for $C_{16}H_6O_4N_2$: C, 55.04; H, 2.75; N, 12.84;
Found: C, 55.04; H, 2.79; N, 13.08.

N-(p-Dimethylaminophenyl)-maleisoimide.—To 2.0 g. (0.0085 mole) of N-(p-dimethylaminophenyl)-maleamic acid in 30 ml. of dry dioxane was added 1.5 ml. (0.01 mole) of trifluoroacetic anhydride. The solution at once turned orange and was kept for five minutes at room temperature. When this solution was poured into 50 ml. of 20 per cent sodium bicarbonate solution, an orange-red precipitate was obtained. The orange-red residue was crystallized from aqueous acetone. Orange needles, m.p. 137 degrees. Yield: 1.6 g. (85 per cent).

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*As the isoimide hydrolyzes very rapidly to the amic acid in presence of trifluoroacetic acid formed as a by-product, the reaction mixture was instead poured in 10 per cent sodium bicarbonate solution to avoid this hydrolysis.

Anal. calcd. for $C_{12}H_{12}N_2O_2$: C, 66.67; H, 5.55; N, 12.96;
Found: C, 66.43; H, 5.72; N, 12.78.

N-1-Naphthylmaleisoimide?—One g. (0.004 mole) of N-1-naphthylmaleamic acid[10] was suspended in 20 ml. of dry dioxane and 1 ml. (0.007 mole) of trifluoroacetic anhydride was added. After one hour, the yellow solution was poured into 50 ml. of 30 per cent sodium bicarbonate solution. The yellow suspension that separated was extracted with ether, and the ether solution was kept over sodium sulfate for 24 hours. The ether was removed under reduced pressure and then kept in a desiccator over sulfuric acid. The infrared spectrum of this dark yellow oil gave two bands at 5.55 and 5.90μ in the carbonyl region which are characteristic of an isoimide. The purification and elemental analysis could not be completed in time to be included in this report.

C. Malonic Series

N-Phenylmalonimide.—Two g. (0.011 mole) of N-phenylmalonamic acid (malonanilic acid)[19] was dissolved in 20 ml. of dry dioxane and 2 ml. (0.014 mole) of trifluoroacetic anhydride was added. The solution at once turned yellow and was kept at room temperature for five minutes. On pouring the solution into ice water, a light yellow precipitate was obtained. The precipitate was filtered and washed first with water and then with 10 per cent sodium bicarbonate solution to remove any unchanged acid. The precipitate was crystallized from a solution of acetone and alcohol. White, fluffy powder, m.p. 210 degrees (reported m.p. 249 degrees). Yield: 1.4 g. (77 per cent). The melting point was not sharp and could not be purified in time to be included in this report.

The infrared spectrum of this product gave the carbonyl band at 5.93μ with a shoulder at 5.70μ; there was no N-H absorption. This showed the presence of an imide.

Anal. calcd. for $C_9H_7NO_2$: C, 67.08; H, 4.35; N, 8.70;

Found: C, 66.63; H, 5.05; N, 8.49.

D. Succinic Series

Succinic dianilide.—Succinanilic acid formed succinic dianilide when it was treated with trifluoroacetic anhydride.[7]

E. Glutaric Series

N-Phenylglutaramic anhydride.—To a solution of 2.00 g. (0.01 mole) of N-phenylglutaramic acid[20] in 15 ml. of dry dioxane was added 1.5 ml. (0.01 mole) of trifluoroacetic anhydride. After one hour at room temperature, the colorless solution was poured into 20 ml. of ice water. The colorless precipitate, which slowly formed on standing was collected and treated with 10 per cent aqueous sodium bicarbonate to remove unchanged acid. Crystallization from ethanol gave 0.72 g. (40 per cent) of crystals, m.p. 145 degrees.

The infrared spectrum exhibited three bands in the carbonyl region at 5.55, 5.75, and 6.05μ, and also an N-H band at 2.98μ, indicating that the product was not the expected isoimide or even an imide. It was tentatively assigned the anhydride structure based on the spectrum.

To confirm the assigned structure, 1.0 g. of the product was hydrolyzed by heating with 15 ml. of 20 per cent sodium hydroxide solution until solution was complete. The cooled solution was acidified with dilute hydrochloric acid and evaporated in the open to give colorless needles of N-phenylglutaramic acid, m.p. 126 degrees, not depressed on mixing with the pure amic acid, and possessing an infrared spectrum identical with that of the known acid.

Reaction of 1.0 g. of the product with 0.5 ml. of aniline in 20 ml. of acetone was carried out by heating the mixture on a steam bath for ten minutes. The reaction mixture was cooled, poured into cold water, and the precipitate was collected. Crystallization from ethanol gave colorless crystals of glutaric dianilide, m.p. 223 degrees (reported for glutaric dianilide[21] m.p. 223 degrees). Evaporation of the aqueous acetone filtrate yielded colorless crystals of N-phenylglutaramic acid, m.p. 126 degrees, again confirmed by infrared spectrum and mixture m.p.

Anal. calcd. for $C_{11}H_{11}NO_2$ (Expected isoimide): C, 69.84; H, 5.82; N, 7.40;

Anal. calcd. for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07;
(anhydride)

Found: C, 66.52; H, 6.09; N, 6.88.

N-(p-Methoxyphenyl)-glutaramic anhydride.—Dehydration of N-(p-methoxyphenyl)-glutaramic acid[22] by trifluoroacetic anhydride gave a 50 per cent yield of the dimeric anhydride, m.p. 159 degrees. The structure was demonstrated by hydrolysis and by ammonolysis with p-anisidine, the expected products (amic acid and amic acid plus dianisidide, respectively) being obtained.

Anal. calcd. for $C_{24}H_{28}N_2O_7$: C, 63.16; H, 6.14; N, 6.14;

Found: C, 62.56; H, 5.95; N, 6.17.

F. Adipic Series

N-Phenyladipamic anhydride.—Dehydration of N-phenyladipamic acid[23] with trifluoroacetic anhydride gave a 50 per cent yield of the dimeric anhydride, m.p. 135-138 degrees. The presence of anhydride was confirmed as before by hydrolysis and ammonolysis.

Anal. calcd. for $C_{24}H_{28}N_2O_5$: C, 67.90; H, 6.60; N, 6.60;

Found: C, 66.58; H, 6.51; N, 6.60.

G. Itaconic Series

N-(p-Methoxyphenyl)-β-(diphenyltrifluoroacetoxymethyl)-succinisoimide?—Two g. (0.0049 mole) of N-(p-methoxyphenyl)-β-(diphenylhydroxymethyl)-succinamic acid was dissolved in 10 ml. of dry dioxane and 1 ml. (0.007 mole) of trifluoroacetic anhydride was added. The solution at once turned yellow and was poured into ice water after five minutes. The yellow semisolid precipitate that separated was washed with 10 per cent sodium bicarbonate solution and was kept in the open for 2-3 hours when it turned solid. This yellow solid was crystallized from acetone with difficulty and gave a product, m.p. 169-170 degrees. Yield: 1.2 g. (51 per cent).

Anal. calcd. for $C_{24}H_{19}O_3N$: C, 78.05; H, 5.15; N, 3.79;

Found: C, 67.39; H, 4.19; N, 3.46.

The elemental analysis of this compound did not agree with the calculated values. The infrared spectrum gave two bands at 5.55 and 5.78μ, which could be due to isoimide. A band at 6.08 could not be due to amide since there was no absorption due to N-H. The product decolorized potassium permanganate solution which shows that the 6.08 band could be due to a double bond. The molecular weight, determined cryoscopically in benzene, was 450.

In order to elucidate the structure of the above compound, it was hydrolyzed by dilute sodium hydroxide solution which regenerated the amic acid, N-(p-methoxyphenyl)-β-(diphenylhydroxymethyl)-succinamic acid. The infrared spectrum of the above compound was almost identical with that of the original amic acid, and the melting point also was not depressed on mixing with the pure acid.

When this regenerated acid was treated with trifluoroacetic anhydride above, it gave a yellow solid which on crystallization from acetone formed yellow shining crystals, m.p. 171 degrees.

Anal. found for this compound: C, 64.48; H, 4.11; N, 2.65;

Anal. calcd. for N-(p-methoxyphenyl)-β-(diphenyltrifluoroacetoxymethyl)-succinisoimide: C, 64.62; H, 4.15; N, 2.89.

From the analysis it appears, therefore, that the product could be N-(p-methoxyphenyl)-β-(diphenyltrifluoroacetoxymethyl)-succinisoimide. The two bands in the infrared region at 5.55 and 5.78 μ are consistent with the isoimide structure.

III. Action of Heptafluorobutyric Anhydride on Amic Acids

A. Phthalic Series

N-(p-Methoxyphenyl)-phthalisoimide.—Two g. (0.0075 mole) of N-(p-methoxyphenyl)-phthalamic acid was dissolved in 35 ml. of dry dioxane. To this mixture, 2 ml. (0.0080 mole) of heptafluorobutyric anhydride was added. The yellow solution was kept for one hour and was then poured into 100 ml. of ice water. The yellow precipitate, which formed after some time, was washed thoroughly with water, and the unchanged acid was removed by keeping the solid in 10 per cent sodium bicarbonate solution for thirty minutes. The yellow residue on crystallization from aqueous acetone gave fine yellow needles. Yield: 1.2 g. (65 per cent); m.p. 134 degrees (reported m.p. 134 degrees).[7] The infrared spectrum of this compound was identical with that of the known isoimide.

B. Maleic Series

N-(p-Methoxyphenyl)-maleisoimide.—On applying the above procedure to N-(p-methoxyphenyl)-maleamic acid, N-(p-methoxyphenyl)-maleisoimide was obtained. Yield: 45 per cent; m.p. 71 degrees. (Reported m.p. 71 degrees.)[7]

The isoimide structure was confirmed by infrared spectrum and mixture m.p.

C. Malonic Series

N-Phenyl-malonimide. When the above procedure was applied to N-phenylmalonamic acid (malonanilic acid), N-phenyl-malonimide was obtained in the form of a white powder. Yield 60 per cent; m.p. 210 degrees.

The compound was identical with the product obtained from trifluoroacetic anhydride and N-phenylmalonamic acid.

D. Succinic Series

Heptafluorobutyranilide.—When 1 g. (0.0051 mole) of N-phenylsuccinamic acid (succinanilic acid) in 20 ml. of dioxane was treated with 1.5 ml. (0.0051 mole) heptafluorobutyric anhydride, it formed

30 per cent of heptafluorobutyranilide, m.p. 85 degrees (m.p. reported, 92 degrees).[24] The product was independently prepared by heating aniline with heptafluorobutyric anhydride. Infrared spectrum and mixture melting point further confirmed that the product was heptafluorobutyranilide.

p-Methoxyheptafluorobutyranilide.—One g. (0.0045 mole) of N-(p-methoxyphenyl)-succinamic acid[7] when treated with 1.5 ml. (0.0055 mole) of heptafluorobutyric anhydride in 15 ml. dioxane gave 0.3 g. (21 per cent) of colorless needles, m.p. 97 degrees. The infrared spectrum indicated a simple amide (N-H at 2.98 and C=O at 5.91) suggesting that acyl exchange had occured. p-Methoxyheptafluorobutyranilide (p-heptafluorobutyranisidide) was prepared from p-anisidine and heptafluorobutyric anhydride; it melted at 97 degrees and gave an infrared spectrum identical with that of the above product.

E. Glutaric Series

N-Phenylglutaramic anhydride.—Dehydration of N-phenylglutaramic acid[20] by heptafluorobutyric anhydride gave a 55 per cent yield of the dimeric anhydride, m.p. 145 degrees, identical with the product obtained from the action of trifluoroacetic anhydride on N-phenylglutaramic acid.

F. Adipic Series

N-Phenyladipamic anhydride.—N-phenyladipamic acid[23] on treatment with heptafluorobutyric anhydride also gave, in 50 per cent yield, the dimeric anhydride, identical in all respects with the product obtained from the action of trifluoroacetic anhydride on N-phenyladipamic acid.

IV. Rate of Dehydration of Amic Acids Using Trifluoroacetic Anhydride as a Dehydrating Agent

N-Phenyl and N-(p-methoxyphenyl)-phthalamic acids were chosen for preliminary study. In each case equimolar quantities of the two acids were dissolved in the same volume of dry dioxane in separate volumetric flasks suspended in a constant temperature bath (30 degrees), and trifluoroacetic anhydride was added at zero time. The amount of isoimide obtained on pouring equal aliquots of the solution in 10 ml. of cold 10 per cent sodium bicarbonate solution at various intervals (10 minutes to one hour) was determined by collecting and weighing the precipitates. The precipitates were dried at 65 degrees in the oven.

V. Tables

The percentage yields from N-phenylphthalamic and N-(p-methoxyphenyl)-phthalamic acids at different reaction times have been listed in Table 1.

The physical properties of the amic acids along with the properties of the corresponding imides and diamides are listed in Table 2.

The isoimides with their melting points, colors and yields are listed in Table 3.

The products obtained from saturated amic acids along with their yields are listed in Table 4.

TABLE 1

EFFECT OF REACTION TIME IN THE DEHYDRATION OF N-PHENYL AND N-(p-METHOXYPHENYL)-PHTHALAMIC ACIDS BY TRIFLUOROACETIC ANHYDRIDE AT 30 DEGREES .

Time, Minutes	% Yield of Isoimide Formed from Phthalanilic Acid	% Yield of Isoimide Formed from N-(p-methoxyphenyl)-Phthalamic Acid
10	32.7	73.1
20	33.8	72.2
30	32.0	72.8
40	34.2	72.0
50	33.6	72.5
60	33.9	73.2
70	34.3	73.8
80	32.9	72.7
90	33.0	71.9
100	32.8	73.0

TABLE 2

PHYSICAL PROPERTIES OF AMIC ACIDS, IMIDES AND DIAMIDES

Substituent	Amic Acid Color*	Imide m.p.* Color	Diamide m.p.* Color
Phthalic Series			
N-(p-nitrophenyl)	192 degrees[15] W	262-264 degrees[15] W	232-234 degrees[25] W
N-(m-nitrophenyl)	202 degrees[15] G	242-244 degrees[15] W	232-234 degrees[25] W
N-(o-nitrophenyl)	149-151 degrees[15] Y	202-203 degrees[15] W	180-184 degrees[25] W
N-(p-dimethylamino-phenyl)	261-264 degrees G	255 degrees[26] Y	--
N-(o-methoxyphenyl)	168-169 degrees[16] W	155-156 degrees W	--
Maleic Series			
N-(p-nitrophenyl)	204 degrees d[17] Y	167-168 degrees[27] Y	--
N-(m-nitrophenyl)	206 degrees d[17] W	126-127 degrees[27] W	--
N-(o-nitrophenyl)	134 degrees[18] Y	130-131 degrees[27] Y	--
N-(p-dimethylamino-phenyl)	212 degrees R	151-154 degrees B	
Malonic Series			
N-phenyl	132 degrees[19] W	249 degrees[19] Y	225 degrees[19] W
Succinic Series			
N-phenyl	150 degrees[28] W	156 degrees[29] W	230 degrees[30] W

TABLE 2 Continued

Substituent	Amic Acid Color*	Imide m.p.* Color	Diamide m.p.* Color
Succinic Series (Continued)			
N-(p-methoxyphenyl)	168-169 degrees[7] W		--
Glutaric Series			
N-phenyl	126 degrees[20] W	144-145 degrees[29] W	223 degrees[21] W
N-(p-methoxyphenyl)	143 degrees[22] W		
Adipic Series			
N-phenyl	151-153 degrees[23] W	--	240-241 degrees[23] W
β-Diphenylhydroxymethyl Succinic Series			
N-(p-methoxyphenyl	138 degrees W	--	--
γ,γ-diphenylitaconic Series			
N-(p-methoxyphenyl)	--	194-195 degrees W	--

*m.p.'s are literature values except where no reference is given.

W = white; Y = yellow; B = brown; R = red; G = grey.

TABLE 3

PHYSICAL PROPERTIES OF PHTHALISOIMIDES AND MALEISOIMIDES

Substituent	Melting Point	Color	Yield, %
Phthalic Series			
N-(p-nitrophenyl)	172 degrees	white	91
N-(m-nitrophenyl)	138 degrees	white	50
N-(o-nitrophenyl)	162 degrees	white	60
N-(p-dimethylaminophenyl)	170 degrees	orange	55
N-(o-methoxyphenyl)	121-122 degrees	yellow	70
Maleic Series			
N-(p-nitrophenyl)	110-112 degrees	light yellow	80
N-(m-nitrophenyl)	57 degrees	yellow	50
N-(o-nitrophenyl)	107-109 degrees	white	82
N-(p-dimethylaminophenyl)	137 degrees	orange	85

TABLE 4

PRODUCTS OBTAINED BY THE ACTION OF TRIFLUOROACETIC ANHYDRIDE AND HEPTAFLUOROBUTYRIC ANHYDRIDE ON SATURATED AMIC ACIDS

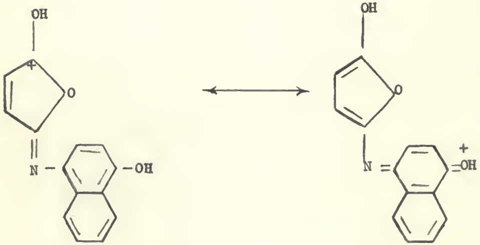
Amic Acid	Products Obtained With Trifluoroacetic Anhydride	M.p. and Yield	Products Obtained With Heptafluorobutyric Anhydride	M.p. and Yield
N-phenylmalonamic	N-phenylmalonimide	210 degrees (77%)	N-phenylmalonimide	210 degrees (60%)
N-phenylsuccinamic	Succinic dianilide	230 degrees (30%)	Heptafluorobutyranilide	85 degrees (30%)
N-(p-methoxyphenyl) Succinamic	Amic acid recovered	--	Heptafluorobutyr-p-anisidide	97 degrees (21%)
N-phenylglutaramic	N-phenylglutaramic anhydride	145 degrees (40%)	N-phenylglutaramic anhydride	145 degrees (40%)
N-(p-methoxyphenyl)-glutaramic	N-(p-methoxyphenyl)-glutaramic	159 degrees (50%)	N-(p-methoxyphenyl)-glutaramic anhydride	159 degrees (55%)
N-phenyladipamic	N-phenyladipamic anhydride	138 degrees (50%)	N-phenyladipamic anhydride	135-138 degrees (50%)

IV. RESULTS AND DISCUSSION

A. Effects of Nitro Substituents, Unsaturation, and Steric Factors on the Dehydration of Amic Acids

While studying the effect of an electron withdrawing group, the nitro group in the ortho, meta, and para positions of the benzene ring in N-arylamic acids, it was found that N-(o,m and p-nitrophenyl)-maleamic and phthalamic acids all formed isoimides when they were treated with trifluoroacetic anhydride. In the case of N-(m-nitrophenyl)-maleisoimide, the usual procedure of recovery of the isoimide had to be altered slightly since the isoimide seemed to hydrolyze quickly to the amic acid in the presence of the trifluoroacetic acid formed as a by-product. The isoimide was therefore recovered by pouring the reaction mixture into ice cold 10 per cent sodium bicarbonate solution, instead of into ice water, and then extracting the isoimide with ether. No difficulty was, however, experienced in the formation of N-(m-nitrophenyl)-phthalisoimide.

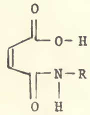
The hydrolysis of N-(m-nitrophenyl)-maleisoimide in the presence of acids is in agreement with the view of Cotter[11] who suggests that the isolation of maleisoimides, such as N-(5-hydroxy-1-naphthyl)- and N-(1-naphthyl)-maleisoimides, should not be possible as they would hydrolyze in the presence of trifluoroacetic acid formed during the reaction. He explains the formation of N-(4-hydroxy-1-naphthyl)-maleisoimide from trifluoroacetic anhydride as due to the isoimide and/or its protonated form being stabilized by resonance, as shown:



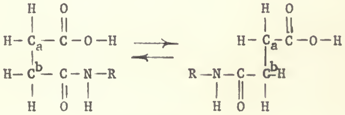
But the author has prepared eight maleisoimides (including N-(1-naphthyl)-maleisoimide)and eleven phthalisoimides in 70-90 per cent yield using only trifluoroacetic anhydride, and therefore it appears that the hydrolysis, which must take place during the work-up procedure (i.e., when the reaction mixture is poured into ice water) is generally not so rapid as to cause difficulty in isolation. This hydrolysis was prevented by the author in each case by washing the isoimide with 10 per cent sodium bicarbonate solution. The hydrolysis in the case of N-(m-nitrophenyl)-maleisoimide was so rapid that, in order to avoid it, the reaction mixture had to be poured directly into 10 per cent sodium bicarbonate solution. It therefore appears that the use of triethylamine as a base, along with trifluoroacetic anhydride as employed by Cotter[11] is unnecessary and does not help in the formation of isoimide, although it does prevent hydrolysis during isolation.

No difficulty was experienced in the formation of isoimides when a strong electron donor group, the p-dimethylamino group, was substituted in the benzene ring of N-arylamic acids.

The action of trifluoroacetic anhydride on saturated amic acids varies with the nature of the acid. N-arylmalonamic, succinamic, glutaramic, and adipamic acids have been treated with this dehydrating agent under the same conditions employed for maleamic and phthalamic acids. Malonanilic acid (N-phenylmalonamic acid) formed N-phenylmalonimide, succinanilic acid (N-phenylsuccinamic acid) gave succinic dianilide while glutaramic and adipamic acids formed dimeric anhydrides. The reason why saturated amic acids could not be dehydrated to isoimides may involve steric factors; that is, these saturated amic acids unlike the unsaturated amic acids (phthalamic and maleamic) have free rotation around carbon atoms a and b as shown:



Unsaturated acid



Saturated acid

Thus, the possibility of the carboxyl and amide groups (or the intermediate formed by reaction with the dehydrating agent) forming a ring is greatly reduced. At the same time, the size of the ring plays quite an important part in the formation of isoimides. A similar effect of size of ring has been observed by Bruice[31] and Thamm[32] in the formation and solvolysis of cyclic acid anhydrides. In order to form an isoimide ring there will be a considerable strain in the lower carbon series like malonic and succinic, but as the ring gets larger the strain is also greatly reduced; but still dimeric anhydrides were obtained from adipic and glutaric series.

In order to account for these different products, it is helpful to consider possible mechanisms of dehydration. It is likely that the N-arylamic acid first forms a mixed anhydride by reaction with the dehydrating agent.[33] The mixed anhydride then combines with another molecule of amic acid to form a dimeric anhydride or it undergoes intramolecular cyclization to isoimide or imide. A second pathway to the formation of isoimide is by intramolecular reaction of the dimeric anhydride. The reason why in some cases the reaction proceeds to the dimeric anhydride and in other cases proceeds to isoimide or imide involves the size of the ring and its stability. In the case of unsaturated amic acids, the isoimide ring is more stable due to resonance than the mixed anhydride or the dimeric anhydride. This type of stabilization is not possible in the case of saturated amic acids, and thus they either form dimeric anhydrides or imides. All these steps along with likely paths of the formation of other products are shown in Fig. 1.

B. Isoimide from a Saturated Acid

While trying to prepare N-(p-methoxyphenyl)-γ,γ-diphenylitaconamic acid IX (which although it is a derivative of succinic acid should give a resonance stabilized isoimide) from γ,γ-diphenyl itaconic anhydride and p-anisidine in benzene, a white product was obtained after purification which melted at 138 degrees and appeared to lack a double bond as it did not decolorize potassium permanganate solution readily. It showed the presence of alcoholic OH in the infrared spectrum which suggested that it was not the expected unsaturated compound IX. Elemental

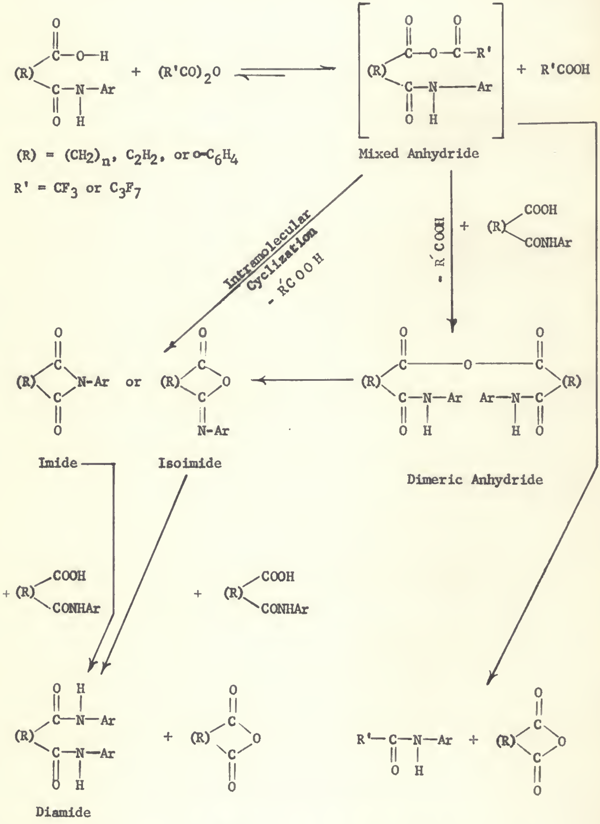
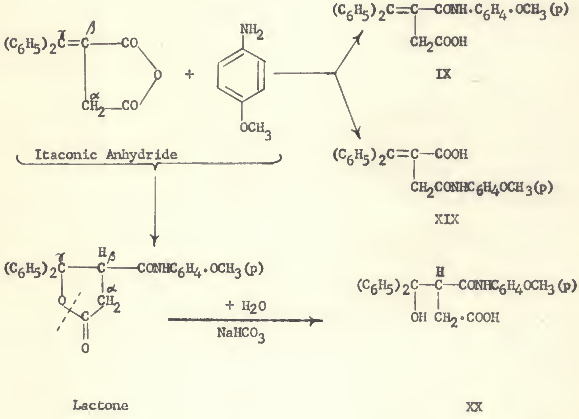


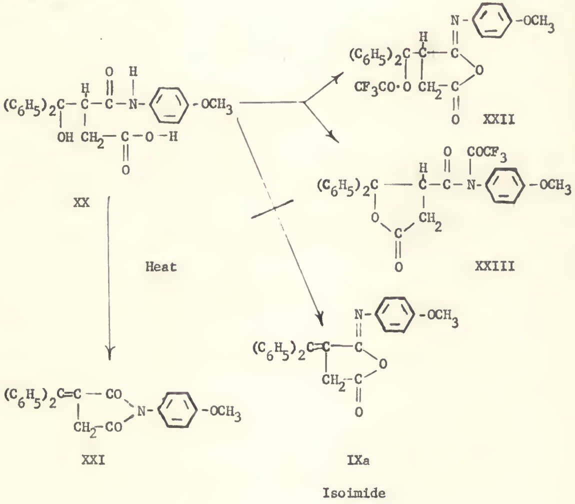
FIG. 1. POSSIBLE MECHANISM OF DEHYDRATION OF AMIC ACIDS BY CARBOXYLIC ACID ANHYDRIDES

analysis further confirmed that it was a hydrated form of IX or XIX. The product was, therefore, assumed to be N-(p-methoxyphenyl)-β-(diphenylhydroxymethyl)-succinamic acid XX. The reason why this product was not assigned the hydrated structure based on XIX is that the reaction of diphenylitaconic anhydride with p-anisidine probably forms a lactone as an intermediate product, and this in the presence of dilute sodium bicarbonate solution is hydrolyzed to XX. Lactonization is possible only when the carboxyl group is attached to the α-carbon of the amic acid. This pathway also determines that the hydroxyl group of the "hydrated" amic acid will be attached to the -γ- rather than to the -β-carbon atom. All these reactions are shown below:



On treating N-(p-methoxyphenyl)-β-(diphenylhydroxymethyl)-succinamic acid XX, believed at the time to be the expected unsaturated amic acid, with trifluoroacetic anhydride by the usual procedure, a yellow semisolid was obtained which solidified after some time. It was crystallized with difficulty from acetone to give a deep yellow product melting at 169 degrees. The infrared spectrum had no N-H or O-H bands and showed two strong bands at 5.65 and 5.79μ. From the spectrum it appeared to be an isoimide. On hydrolysis with dilute sodium hydroxide, it regenerated the original amic acid XX which is quite characteristic of all isoimides, which are rapidly hydrolyzed to the original acids. From this evidence it appeared to be an isoimide, but elemental analysis gave the percentages of carbon, hydrogen, and nitrogen as 67.39, 4.19, and 3.46, respectively. (Calculated for isoimide C, 78.05; H, 5.15; and N, 3.79.) Since this compound had strong absorption between 8 and 9 microns, it was decided to test for fluorine. The fluorine test was inconclusive. In order to obtain more evidence, the hydrated amic acid was heated. The product showed imide bands in the infrared spectrum and the elemental analysis further confirmed it to be N-(p-methoxyphenyl)-γ,γ-diphenylitaconimide XXI. As the yellow compound obtained from XX and trifluoroacetic anhydride did not crystallize well, it was thought to be a mixture, but it could not be purified further by crystallization. However, when the hydrolyzed product of this compound, which was assumed to be the acid XX,was treated again with trifluoroacetic anhydride, it formed a yellow product which, though similar to the original yellow product, was more crystalline and easily crystallizable from acetone. It gave an elemental analysis of C, 64.48; H, 4.11; and N, 2.65.

On the basis of elemental analysis, two structures XXII and XXIII, are possible.



Analysis for fluorine gave 11.94 per cent (Calcd. 11.80 per cent) demonstrating the presence of fluorine and hence of the trifluoroacetyl group. The structure XXII is preferred, as the infrared spectrum of the product has two strong bands at 5.65 (C=O) and 5.82 (C=N). The average molecular extinction coefficients of these bands are 291 and 253, respectively, which are close to the values obtained for known isoimides. (See Section D.) A third band due to the trifluoroacetate, which should absorb at 5.6μ, could not be identified. The isoimide should not be stabilized by resonance, as was originally intended; hence if the product from the action of trifluoroacetic anhydride on N-(p-methoxyphenyl)-β-(diphenylhydroxymethyl)-succinamic acid has the isoimide structure assigned to it, it represents the first example of a succinisoimide, and the only saturated isoimide besides the camphorisoimides.

C. Dehydration Studies

To study quantitatively the effect of substituents on the rate of formation of isoimides, N-phenyl, and N-(p-methoxyphenyl)-phthalamic acids were chosen for preliminary study. It was observed that the yield of isoimide formed remained approximately the same throughout the course of the measurements. The only reasonable conclusion that can be drawn from this experiment is that the reaction was already over (within ten minutes) before the first aliquot was removed from the reaction flask. This procedure was therefore not workable as the reaction time was too short and the recovery of isoimide was not quantitative. The rate studies were not pursued any further.

D. Interpretation of Infrared Data

Since the carbonyl absorptions of amic acids, imides and anhydrides fall in the same region (between 5.4 and 6.2μ), it was decided to compare these with the absorption of isoimides.

The infrared spectra of anhydrides of phthalic[34] and maleic[35] acids contain two carbonyl absorption bands about 0.28 apart:

Maleic Series	5.40μ	5.59μ
Phthalic Series	5.42μ	5.63μ

N-arylphthalimides and N-arylmaleimides have been found to absorb strongly at 5.80-5.81μ, usually with two shoulders in the lower wave length region (5.60-5.61 and 5.73-5.74). The N-arylamic acids give strong bands at 5.90 and 6.10μ and in addition show N-H absorption in the region 3.0-3.1μ.

In general N-arylphthalisoimides and N-arylmaleisoimides give two strong bands at 5.54μ (C=O) and 5.88μ (C=N). All of the carbonyl absorption bands of isoimides prepared in this study and in the previous study, along with other bands characteristic of these compounds, have been listed in Tables 5 and 6. The bands are in agreement with those reported by Carpino, Tsou, and Cotter.

Roderick[36] (unpublished work) has made quantitative studies of the infrared spectra in the region 5-6μ for pairs of imides and isoimides of both the maleic and phthalic series. He has shown that the molecular extinction coefficients of the two absorptions are more characteristic of the type of ring than are the wave lengths, and the technique has been employed to confirm the assignment of the isoimide structure to isoimides which absorb at wave lengths outside the usual range. Thus N-(p-dimethylaminophenyl)-phthalisoimide absorbs at 5.67 and 5.95μ, whereas most phthalisoimides absorb at 5.55 and 5.85μ, respectively. The molecular extinction coefficients of the two bands of this isoimide were in the range observed for other isoimides and definitely excluded the imide structure. The average molecular extinction coefficients obtained by him have been listed in Table 7.

TABLE 5

INFRARED SPECTRA[a] OF N-ARYL-PHTHALISOIMIDES[b]

ARYL	C=O	C=N	PHENYL	OTHERS
p-dimethylaminophenyl	5.67 s (sh 5.55)	5.95 s	6.28 s	10.82 s
o-methoxyphenyl	5.55 s (sh 5.40)	5.85 s	6.30 s (sh 6.25)	10.90 s
p-methoxyphenyl	5.55 (sh 5.45) (sh 5.60)	5.88 s (sh 5.95)	6.25 m	10.80 s (sh 10.65)
o-tolyl	5.55 s (sh 5.50)	5.83 s	6.23 w	10.75 s
p-tolyl	5.55 s (sh 5.50)	5.85 s	6.20 w	10.81 s
o-chlorophenyl	5.45 s (sh 5.55)	5.85 s	6.21 w	10.85 s
p-chlorophenyl	5.53 s (sh 5.65)	5.91 s	6.25 w	10.90 s
o-nitrophenyl	5.55 s (sh 5.45)	5.80 s	6.25 s	10.70 (sh 10.85)
m-nitrophenyl	5.55 s (sh 5.45) (sh 5.35)	5.85 s	6.20 w	10.60 s 10.80 s
p-nitrophenyl	5.45 s (sh 5.50)	5.80 s	6.28 (sh 6.23)	10.95 s

[a] All spectra obtained in mulls on a Perkin-Elmer Infrared Spectrophotometer, Model 137-B.

[b] All wave lengths in microns; s = strong, m = medium, w = weak, sh = shoulder.

TABLE 6

INFRARED SPECTRA[a] OF N-ARYL-MALEISOIMIDES[b]

ARYL	C=O	C=N	PHENYL	C=C	OTHERS
p-dimethylaminophenyl	5.68 s (sh 5.60)	5.95 m	6.30 s	6.05	10.56 11.10
p-methoxyphenyl	5.55 s	5.62	6.29 s	6.01	10.92 11.18
p-ethoxyphenyl	5.55 s (sh 5.50) (sh 5.78)	6.00	6.25 s	6.10 w	11.00 11.09
p-tolyl	5.62 (sh 5.55)	5.92	6.30	6.20 w	11.00 11.18
o-nitrophenyl	5.52 (sh 5.56)	5.85	6.25	6.10 w	10.85 11.30
m-nitrophenyl	5.57 (sh 5.50) (sh 5.75)	5.92	6.20 w	6.01 w	11.00
p-nitrophenyl	5.60 (sh 5.55)	5.96	6.28 (sh 6.31)	6.10 w	10.96 11.28

[a] All spectra obtained in mulls on a Perkin-Elmer Infrared Spectrophotometer, Model 137-B.

[b] All wave lengths in microns; s = strong, m = medium, w = weak, sh = shoulder.

TABLE 7

AVERAGE MOLECULAR EXTINCTION COEFFICIENTS OF IMIDE AND ISOIMIDE

Series	λ_1	ϵ_1	λ_2	ϵ_2
Phthalimides	5.73	294	5.80	1149
Phthalisoimides	5.54	354	5.88	367
Maleimides	Absent	---	5.80	848
Maleisoimides	5.56	436	5.84	214
N-(p-methoxyphenyl)-diphenylitaconimide	5.65	175	5.82	762
N-(p-methoxyphenyl)--(diphenyltrifluoro-acetoxymethyl)-succinisoimide	5.58	291	5.78	253

From the above values it can be concluded that the average ϵ at 5.80μ (λ_2) for an isoimide is around 300 and for an imide around 900.

E. Attempted Studies on the Detection of Enolic Form

In order to study whether amic acids exist in the enolic form in any appreciable concentration; it was decided to detect the presence of enolic form in N-(p-methoxyphenyl)-phthalamic acid by means of nuclear magnetic resonance spectra. As the chemical shift of the carboxylic hydroxyl in this acid was likely to interfere with the chemical shift of hydroxyl of the enolic form, the methyl ester of this acid was prepared using diazomethane. The results obtained from nuclear magnetic resonance spectra* were inconclusive, as the compound was not sufficiently soluble in carbon tetrachloride but suggested the absence of enol. The temperature change also did not show the presence of any enolic form.

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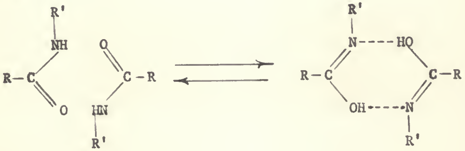
*The author is thankful to Dr. W. S. Brey, Jr., for obtaining and for the interpretation of the nuclear magnetic resonance spectra.

The infrared spectra of the methylester could not be obtained in non-hydroxylic solvents like carbon tetrachloride or dioxane due to its insolubility in these solvents. However, the spectrum obtained in mull did not show any enolic OH. Buswell,[37] while studying the infrared spectra of substituted and unsubstituted amides, found that as the concentration of solute was increased, the association through hydrogen bonding increased, and this is accompanied by a considerable amount of enolization.



He obtained all his spectra in carbon tetrachloride and found that with increase in concentration, the association through hydrogen bonding increased and this in turn increased the absorption due to hydrogen bonded N-H. The unbonded N-H peaks were reduced in intensity but otherwise unmodified. As N-(p-methoxyphenyl)-phthalamic ester was insoluble in carbon tetrachloride, spectra were obtained at different concentrations in nujol. The unbonded N-H peaks were not reduced in intensity as expected, and no absorption due to hydrogen bonded N-H appeared. It therefore appears that there is no enolic form present.

F. Action of Heptafluorobutyric Anhydride on Amic Acids

As stated above, the action of trifluoroacetic anhydride on unsaturated and saturated amic acids was studied. Since it did not effect dehydration of succinamic acids, heptafluorobutyric anhydride, which is a stronger dehydrating agent, was tried on these and other saturated amic acids. In the case of succinamic acids, instead of dehydration by heptafluorobutyric anhydride acyl exchange occurred. Thus, N-phenylsuccinamic acid gave heptafluorobutyranilide and N-(p-methoxyphenyl)-succinamic acid gave p-heptafluorobutyranisidide. A similar exchange has been reported for the treatment of maleamic acids with acetic anhydride[38] and for the action of trifluoroacetic anhydride on peptides.[39] The products obtained from other saturated amic acids, malonamic, glutaramic, and adipamic acids, were the same as those obtained when trifluoroacetic anhydride was used as a dehydrating agent. N-phenylmalonamic acid gave N-phenylmalonimide while N-phenylglutaramic, N-(p-methoxyphenyl)-glutaramic and N-phenyladipamic acids were converted to their respective dimeric anhydrides.

The action of this dehydrating agent on unsaturated amic acids, however, is again to effect dehydration to the isoimides. Thus, N-(p-methoxyphenyl)-phthalamic and maleamic acids were dehydrated to the corresponding isoimides, although the yields as compared to the yields of isoimides obtained from trifluoroacetic anhydride were considerably lower.

The various products obtained with these two dehydrating agents have been summarized in Table 8. The different products obtained by heptafluorobutyric anhydride from both saturated and unsaturated amic

TABLE 8

PRODUCTS OBTAINED BY THE ACTION OF TRIFLUOROACETIC ANHYDRIDE AND HEPTAFLUOROBUTYRIC ANHYDRIDE ON SATURATED AMIC ACIDS

Amic Acid	Products Obtained With Trifluoroacetic Anhydride	Products Obtained With Heptafluorobutyric Anhydride
N-phenylmalonamic	Imide	Imide
N-phenyl-succinamic	Dianilide	Heptafluorobutyranilide
N-(p-methoxyphenyl)-succinamic	Amic acid recovered	Heptafluorobutyranisidide
N-phenylglutaramic	Dimeric anhydride	Dimeric anhydride
N-(p-methoxyphenyl)-glutaramic	Dimeric anhydride	Dimeric anhydride
N-phenyladipamic	Dimeric anhydride	Dimeric anhydride

acids can again be explained if it is assumed that the reaction follows the paths shown in Fig. 1.

On comparing these two dehydrating agents for the synthesis of isoimides, trifluoroacetic anhydride should be preferred over heptafluorobutyric anhydride as the products obtained were in much better yields, and the former reagent is less susceptible to hydrolysis on standing.

G. Basicity of Isoimides

When dry hydrogen chloride was bubbled through ethereal solutions of different maleisoimides, orange-yellow hydrochlorides were formed immediately. On keeping them in air for a short time they were hydrolyzed to amic acids. However, some difficulty was encountered in forming hydrochlorides of phthalisoimides. These seem to hydrolyze very rapidly to amic acid even in the least amount of moisture.

It is believed that this property (basicity) of isoimides can be utilized for separating or purifying an isoimide from a mixture of an isoimide and imide. It should also be a good tool for distinguishing an isoimide from an imide by chemical means.

As not much time was spent on this part of the problem, it is recommended that more comprehensive studies on the basicity of isoimides might be profitable.

V. SUMMARY

In a previous investigation, by the author, a series of N-arylphthalisoimides and maleisoimides were synthesized using trifluoroacetic anhydride as a dehydrating agent. In a continuation of the same work a study was made of the effects of strong electron withdrawing and donating groups (nitro and dimethylamino groups, respectively) in the amine moiety, unsaturation in the acid moiety, the use of strong dehydrating agents, and steric factors (such as the size of the ring formed) on the dehydration of these amic acids.

It was found that with the exception of m-nitrophenyl maleisoimide, no difficulty was experienced in the formation of isoimides. This isoimide hydrolyzes rapidly to the amic acid, and hence a different technique was employed for its isolation.

The effect of different substituents on the rate of formation of isoimides could not be measured owing to experimental difficulties. It was, however, evident from the experiment that the formation of isoimide was complete in less than ten minutes at 30 degrees.

From the infrared spectra of N-arylphthalisoimides and maleisoimides, it was found that C=N and C=O of cyclic isoimides absorb at 5.88 and 5.54 , respectively.

The actions of trifluoroacetic anhydride and heptafluorobutyric anhydride on saturated N-arylamic acids are similar except in the case of N-arylsuccinamic acids. Both dehydrating agents formed imides from malonamic acid, while glutaramic and adipamic acids gave their respective dimeric anhydrides. N-phenylsuccinamic acid with trifluoroacetic anhydride formed dianilide, but N-(p-methoxyphenyl)-succinamic acid was recovered unchanged. In the case of heptafluorobutyric anhydride, instead of dehydration, acyl exchange occurred, and N-phenyl and N-(p-methoxyphenyl)-succinamic acids formed heptafluorobutyranilide and heptafluorobutyranisidide, respectively.

As enolic form could not be detected in the N-arylamic acids prepared in this study, the formation of isoimides in general does not seem to go through the enolic form as was suggested by Tsou. Since the presence of a base is necessary for the formation of the cyclic intermediate proposed by Cotter, the mechanism of formation of isoimides does not seem to follow this path either. A possible mechanism of dehydration of amic acids involves the formation of a mixed anhydride from the N-arylamic acid and trifluoroacetic or heptafluorobutyric anhydrides. This mixed anhydride is then converted to an imide, isoimide, or dimeric anhydride. Another possible conversion of the mixed anhydride is to a substituted amide (heptafluorobutyranilide) and acid anhydride.

In an attempt to prepare an unsaturated resonance-stabilized isoimide of the succinic series, a saturated isoimide of the succinic series was obtained. This isoimide is not stabilized by resonance. The isoimide, N-(p-methoxyphenyl)-β-(diphenyltrifluoroacetoxymethyl)-succinisoimide is the first example of a succinisoimide, and the only saturated isoimide known besides the camphorisoimides.

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BIOGRAPHICAL SKETCH

Parshotam Lal Bhatia was born in Jhanghmaghiana, W. Punjab (West Pakistan), on October 15, 1926. In 1941 he graduated from S. D. High School, Lahore, (W. Pakistan), and entered Hindu College, Delhi, India. From that institution he received his Inter Science degree and entered Meerut College, Meerut, U. P., affiliated with Agra University, Agra, India, and from there he received his Bachelor's and Master's degrees in 1945 and 1947, respectively.

Since 1947, he has been on the staff of Meerut College, Meerut, as lecturer in chemistry. In 1957 he entered the graduate school at the University of Florida and got his Master's degree in August, 1960. From 1957 to 1960 he held a graduate assistantship in the Department of Chemistry, but since 1960 he has been on a research grant provided by the Research Corporation of New York.

This dissertation was prepared under the direction of the chairman of the candidate's supervisory committee and has been approved by all members of that committee. It was submitted to the Dean of the College of Arts and Sciences and to the Graduate Council, and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 1961

Dean, College of Arts and Sciences

Dean, Graduate School

Supervisory Committee:

William R. Roderick
Chairman

W. T. Lippincott

W S Brey

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Lauretta E. Fox